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Microfluidics: A golden opportunity for Positron Emission Tomography?

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Since its introduction in the 1970s, positron emission tomography (PET) has been used to investigate the basic biology and diagnosis of a diverse range of medical conditions in oncology, neurology, psychiatry, cardiology and inflammation. Indeed, to date, there have been well over 1500 biologically active compounds containing positron emitting isotopes such as [^{18}F]fluorine, [^{11}C]carbon or [^{13}N]nitrogen described in the literature [1]. However, today one tracer, [^{18}F]fluorodeoxyglucose (FDG), accounts for more than 90% of all clinical PET scans due to its broad applicability and availability. While other radiotracers have the potential to deliver a more fundamental understanding of the underlying biology of diseases and facilitate the development of new treatments, their production is limited to specialist hospitals and universities.

At the core of the radiopharmaceutical synthesis process is the rapid incorporation of a positron-emitting isotope or synthon into a molecule of interest followed by product purification and formulation. Due to the short half-lives of the radioisotopes used (^{18}F : $t_{1/2} = 110$ min; ^{11}C : $t_{1/2} = 20.4$ min; ^{13}N : $t_{1/2} = 10.0$ min) it is advantageous to incorporate the radioisotope into the molecule of interest as late as possible in the synthetic sequence and have the production facility in close proximity to the PET scanning suite. However, several synthetic steps may be required to transform the radioactive isotope into a reactive form suitable for labeling [2] and the presence of multiple reactive groups on the precursor may also necessitate the use of protecting groups, which must be subsequently removed. Furthermore, since the radiotracers are typically administered intravenously, purification and reformulation processes must also be included to yield pharmaceutical grade materials. Consequently, large amounts of starting radioactivity may be required to compensate for radioactive decay, poor radiolabeling as well as deprotection efficiencies and losses during purification. Due to the high levels of penetrating gamma radiation emitted, specialist automated equipment, lead shielding, radiation containment and air-handling facilities are required, and the delivery of these imaging agents to the wider population remains a challenge. The future utilization of PET may be significantly enhanced, however, by improvements in reagent manipulation techniques, enabling production by nonspecialist radiochemists, and increased radiolabeling efficiency leading to a reduction in the quantities of starting activity required.

Recently, great interest has been generated by the potential advantages of fluid-handling devices with feature sizes most conveniently measured in microns and total volumes typically in the nanoliter range, coined 'microfluidic reactors' [3]. Initially applied to the areas of chemical and biological analysis, microfluidics has enjoyed a surge in popularity in the area of radiochemical synthesis due to inherent advantages associated with miniaturization, which correlate closely with the characteristic deficiencies in conventional macroscale radiosyntheses. Microfluidic reactors have intrinsically high surface area to volume ratios and short mixing distances, which culminate in extremely efficient mass and heat transfer, increasing reaction efficiency and enabling a significant reduction in processing time. An enhancement in reaction rates may also allow a reduction in precursor, solvent and reagent loading, which together can lead to a decrease in the degree of isotopic dilution [4]. The specific activity, the ratio of radioactively labeled product to its nonradioactive equivalent (e.g., ^{11}C vs ^{12}C), is of particular importance in radiosyntheses that employ very short half-life isotopes [5]. Compared with conventional synthesis methodologies, decreased technical handling associated with microfluidic systems is, in

principle, an attractive way to produce higher yielding syntheses. Furthermore, by reducing intrinsic length scales to less than those typically required for positron annihilation, radiolytic degradation of the radiopharmaceutical could be significantly reduced [6].

Initially, microfluidic reactors were the domain of specialists in the field due to the precision fabrication methods, complicated fluid dynamics and technically challenging micro to macro-scale interfacing. Recently however, microfluidic reactors are increasingly becoming commercially available as standalone or modular devices. For the rapid screening of microfluidic radiolabeling conditions, a widely adopted strategy is to employ conventional scale laboratory automation for reagent handling, concentration and reformulation and to employ a microfluidic channel for the radiolabeling step only [7]. Microfluidic devices that operate in this fashion are known as flow-through or continuous-flow devices, where the reaction time is determined by the dimensions of the capillary and the flow rate. This technique does not require that the user have any specialist knowledge of microfluidic design or operation, and by limiting the number of microfluidic interfaces to that of a single capillary, rapid instigation and method development is facilitated [8–10].

However, the amalgamation of simple microscale channels and conventional automation techniques fails to address losses associated with macroscale syringe and fluidic connection dead volumes. In addition, despite the reaction volume being reduced by several orders of magnitude, no reduction in equipment footprint or infrastructure requirement is achieved. Furthermore, despite the improved mass and heat transfer efficiencies provided by microfluidics, benefits to radiosynthesis are not always realized. Where a radiolabeling method exhibits particularly slow reaction kinetics, improvements in mass and heat transfer may fail to offer yield improvements due to a required minimum reaction time [11]. For reactions of this type, a microfluidic device can be operated in a stopped-flow or batch mode [12]. Batch mode devices typically contain a greater degree of miniaturization than flow-through devices, potentially incorporating microvalves, micropumps and reagent storage on a single, fully integrated device [13]. With reaction chamber volumes measured in nanoliters, working with valuable reagents, such as peptides and antibodies, is simplified significantly, reducing losses and precursor cost per synthesis [14]. In contrast to the hybrid automation–microfluidic flow-through reaction systems, these fully integrated miniaturized synthesis devices offer significant reductions in shielding requirements due to their considerably reduced footprint. Microfluidic devices of this type are most frequently fabricated from polymers such as polydimethylsiloxane through micro-molding and lamination techniques. The application of mass production techniques, such as microinjection molding and hot embossing, may also enable microfluidic devices to offer a high degree of regulatory compliance through disposability commonly found in polymeric medical devices. However, with typical cyclotron liquid and gas target volumes ranging from less than 1 to several hundred milliliters, and formulated intravenous solutions ranging from 1 to 10 ml, devices of this nature are currently most suited to preclinical applications. Consequently, advances in methods for concentrating radiolabeled cyclotron products, as well as techniques for the purification and formulation of syntheses, are required. These must be further developed to interface with microfluidic systems to make this technology more accessible for clinical applications [15].

The substitution of conventional automated radiosynthesis equipment for microfluidic reactors alone cannot reduce the manufacturing costs of PET tracers sufficiently to enable its expansion to become an everyday imaging technique such as MRI or CT. Indeed, the application of miniaturization and flow-through synthetic techniques are not new to radiochemistry. Radiolabeling with [^{11}C]methyl iodide within a stainless steel loop is a classic example of a biphasic reaction in a quasi-microfluidic channel, which can be utilized to obtain a number of radiotracers in high yield [16]. Furthermore, the reaction of [^{18}F]fluoride trapped on functionalized polystyrene anion exchange ‘Merrifield’ resin packed in narrow bore tubing was, for a period, the *de facto* method for the manufacture of [^{18}F]FDG [17].

It is clear, therefore, that the miniaturization of instrumentation for radiotracer synthesis offers significant advantages to the radiochemist in increases of reaction efficiency, and reduced development time and cost. Since automated synthesis units for the production of PET radiotracers became commercially available, the development and optimization of reaction variables (time, temperature, concentrations and so forth) has been largely left to the radiochemistry expertise of the end-users. This is desirable in a research setting or where

flexibility of system operation is required. However, with the expansion of the availability of PET and the lack of suitable PET radiochemistry expertise, synthesis device manufacturers are increasingly developing robust synthetic sequences that can be exported to the PET laboratories for use ‘as is’. If the mainstream use of microfluidic technology is to become commonplace, the manufacturers of these devices will be looked to from many quarters of the PET community to take on similar levels of validation and optimization of processes that would require little or no further optimization by the end user.

The universal applicability of microfluidics to PET tracer synthesis remains unsolved however, where issues of integration, slow-reaction kinetics and ability to process useful patient doses continue to present significant challenges. In addition to miniaturizing radiosynthesis, the infrastructure costs associated with the isotope generating cyclotron are also being investigated through the development of miniaturized cyclotrons [18]. By combining these two complementary technologies, the number of hospitals and institutions able to offer both commonly available tracers such as [¹⁸F]FDG, as well as enabling research with new and exciting radioligands, is set to expand significantly in the next few years and may usher in a new era in PET as a widespread clinical tool for the study of human physiology.

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